DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: 510/337-6700

VIA FEDERAL EXPRESS

September 30, 2002

Our Reference No. 3003528540

Mr. Peter B. Kelly
President and Chief Executive Officer
Med-Mart Pulmonary Services
1701 Novato Blvd., Suite 209
Novato, CA 94947

WARNING LETTER

Dear Mr. Kelly:

During an inspection of Med-Mart Pulmonary Services, located at 2929 F Street, Bakersfield, CA, on December 20 and 21, 2001, our investigator observed serious violations of the Federal Food, Drug, and Cosmetic Act (the Act).

As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended the Federal Food, Drug, and Cosmetic Act (the Act) creating Section 503A, *"Application of Federal Law to the Practice of Pharmacy Compounding."* This provision became effective on November 21, 1998, and set forth the requirements that compounded products must meet to qualify for exemption from the new drug (505), certain adulteration (501(a)(2)(B)), and misbranding (502(f)(1)) provisions of the Act.

On February 6, 2001, the United States Court of Appeals for the Ninth Circuit held that the commercial speech restrictions in section 503A violate the First Amendment to the Constitution, and further held section 503A to be invalid in its entirety because the speech restrictions could not be severed from the remainder of the provision. On April 29, 2002, the Supreme Court affirmed the Ninth Circuit Court of Appeals decision. The Court did not rule on, and therefore left in place, the Ninth Circuit's holding that the unconstitutional restrictions on commercial speech could not be severed from the rest of section 503A. Accordingly, all of section 503A is now invalid.

As a result, the agency now utilizes its longstanding policy to recognize and exercise its enforcement discretion for extemporaneous compounding, where reasonable quantities of drugs are manipulated upon receipt of valid prescriptions from licensed practitioners for individually identified patients. The Agency remains seriously concerned, however,

about the public health risks associated with the large-scale production of massive quantities of inhalation solutions without these products being required to meet all the laws and regulations applicable to a drug manufacturer.

This concern exists especially in light of your firm's need to conduct a class I recall of 5 lots of various Albuterol inhalation solutions due to contamination with *Serratia liquefaciens* in December 2001. In addition, FDA found *Bacillus megaterium* in the first lot of Albuterol solution manufactured after these contaminated lots.

Your firm purports to be a compounding pharmacy (as noted in your February 5, 2002, letter to the FDA investigator). However, our investigation has determined that your firm exceeds the scope of the regular course of the practice of pharmacy. Our findings are consistent with the California Board of Pharmacy's letter dated February 8, 2002, which indicates that your firm's activities go beyond that of a pharmacy and into the activities of a drug manufacturer. Our findings include the following:

1. You repeatedly manufacture the same inhalation products in such large quantities that the use of commercial scale equipment is required. You do not have prescription orders on hand for individually identified patients for all requests for compounded drug products that you receive.

2. The California Board of Pharmacy, in its joint inspection with FDA of December 20 and 21, 2001, determined that your firm's activities go beyond that of a pharmacy and involve manufacturing and advised your firm that the Board was referring the matter to the Attorney General's office for action with regard to your manufacturing operations. The California Board based this determination on a number of factors including, but not limited to: 1) these products are furnished to prescribers in California and other states as samples; 2) the quantity of the products manufactured by your firm is very large; and, 3) the equipment utilized by your firm to manufacture these products is commercial scale in size and style. We agree with the Board that these are characteristics that are more representative of a manufacturer rather than a retail pharmacy.

3. The California Board of Pharmacy also issued a Violation Notice to your firm on December 20, 2001, citing a lack of policies and procedures and job description for pharmacy technicians as required by pharmacy law. Your firm employs pharmacy technicians who were assigned job duties that involved the cleaning and monitoring of a complex packaging machine with no documentation of training and a lack of policies and procedures used to standardize processes and to monitor competency to ensure consumer product safety.

4. Batch records indicate that your firm produces batch sizes of [redacted] to [redacted] units, some portion of which is allotted for starter packs. A valid prescription order for identified individual patients is never received for the starter pack medications. Information obtained during the inspection indicated that in one four day period, over [redacted] starter packs (equivalent to over [redacted] units) were provided to physicians. A State

Inspector reported that during the inspection, a pharmacist with your firm stated that no special run or additional amount was added to make up the starter packs. Your firm reportedly siphoned off from a batch run to make up the starter packs requested by physicians. This indicates to us that the amount your firm prepares to cover prescriptions received exceeds the amount needed to fill these prescriptions. It also seems to contradict a statement made by your firm in a December 19, 2001 letter to the California State Board of Pharmacy that your firm has prescriptions on hand before you compound and that you do not engage in anticipatory compounding. This practice appears to go beyond the practice of compounding very limited quantities of drugs in anticipation of receiving prescriptions in relation to amounts of drugs compounded after receiving valid prescriptions.

In light of the above, we do not believe that your firm is operating as a retail pharmacy engaged in extemporaneous compounding that would justify our exercising enforcement discretion. As such, your firm appears to be in violation of the following sections of the Federal Food, Drug, and Cosmetic Act:

Section 505
The inhalation solutions manufactured by your firm are drugs within the meaning of Section 201(g) of the Act. As such, they may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act because these articles are also new drugs within the meaning of Section 201(p) of the Act, and your firm has no approved new drug applications filed pursuant to Section 505(b) or (j) of the Act.

Section 502(f)(1)
Your drug products are misbranded within the meaning of Section 502(f)(1) of the Act in that their labeling fails to bear adequate directions for use for which they are being offered and they are not exempt from this requirement under 21 CFR 201.115 since they are unapproved new drugs.

Section 502(o)
Your drug products are misbranded under Section 502(o) of the Act in that they are manufactured in an establishment not duly registered under Section 510, and the articles have not been listed as required by Section 510(j). Your facility is not exempt from registration and drug listing under 21 CFR 207.10 or Section 510(g) of the Act.

Section 501(a)(2)(B)
Your drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Act in that the controls and procedures used in the manufacture, processing, packing, and holding do not conform to current good manufacturing practices regulations, 21 CFR, Part 210 and 211. Deviations from these regulations include, but are not limited to, the following:

1. Failure to have appropriate laboratory determination of satisfactory conformance to final specifications for your inhalation drug products prior to release [21 CFR

211.165]. Your procedure for manual processing states that samples of [redacted] products will be submitted to an independent laboratory [redacted] for stability and sterility testing. However, chemical and microbial testing is required before each and every lot of product is released for distribution. One specific example of you distributing a product prior to obtaining finished product testing involves Albuterol inhalation solution, lot number 112601NAI. This lot was manufactured on November 26, 2001 and was shipped to patients on December 7-10, 2001. However, the sterility test results, dated December 10, 2001, document that the product had microbial contamination. This contamination resulted in a Class I recall for this lot and four others that were similarly contaminated. The contamination of these lots results in adulteration violations under 501(c) of the Act.

2. Failure to designate a quality control unit, or person, authorized to perform Quality Control functions and responsibilities [21 CFR 211.22]. For example, five lots of Albuterol combination inhalation solution were distributed prior to receiving analytical results, which indicated microbial contamination of the lots.

3. Failure to establish appropriate written procedures or processes designed to prevent objectionable microorganisms in drug products not required to be sterile [21 CFR 211.113(a)]. Specifically, your written procedures, which require equipment and manufacturing areas to be cleaned with [redacted] solution, did not prevent at least three Albuterol combination inhalation solution lots (112601LAC, 112801AAI, and 112901AAI) from becoming contaminated with pathogenic microorganisms (as defined by your contract laboratory). Other lots were also found to be contaminated, but your analysis did not determine pathogenicity. At the time these inhalation solutions were made, they were not required by regulation to be sterile. However, as of May 27, 2002, all aqueous-based drug products for oral inhalation must be manufactured to be sterile [21 CFR 200.51]. Manufacturers of such products must also comply with the requirements of 21 CFR 211.113(b) (Control of microbiological contamination). The controls you currently have in place are inadequate to ensure product sterility.

4. Failure to establish written procedures for production and process control designed to assure that the inhalation drug products have the identity, strength, quality and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example, you have no evidence that your manual mixing steps, filtration, dispensing and labeling operations will function as expected for the types of drug products manufactured.

5. Failure to document the failure of a batch to meet any of its specifications and to make a record of the investigation, including conclusions and follow-up [21 CFR 211.192]. For example, after a private laboratory notified you that at least five lots of Albuterol combination inhalation solutions tested positive for microbial contamination you did not document any investigation or corrective actions.

6. Failure to perform routine calibration and to assure proper performance of all automatic, mechanical, and electronic equipment used in the manufacture, processing,

packing, and holding of a drug product [21 CFR 211.68]. For example, your filtration unit, [redacted] small batch filler unit, industrial scale, [redacted] Pump, and the [redacted] Machine used to fill, label, and seal drug products have not been calibrated or otherwise checked to ensure they perform their operations consistently and accurately.

7. Failure to establish complete batch production and control records for each drug product, and for each batch size [21 CFR 211.188]. For example, the record for lot number: 111201AAF, Exp.: Feb 12, 02 for Albuterol 2.5 mg/ Ipratropium 0.5mg, does not reflect that each significant step was done; is not dated; lacks the actual weights and measures of components used in the course of processing; does not identify individual major equipment and lines used; does not mention in-process or laboratory results; bears no statement of actual vs. theoretical yield; lacks a description of any labeling control records; does not indicate if any sampling was performed; and, does not identify the persons performing and directly supervising or checking each significant step.

8. Failure to establish an adequate stability testing program, which includes an adequate sample size and test interval based on statistical criteria for each attribute examined to assure valid estimates of stability [21 CFR 211.166]. Specifically, your procedure for manual processing states that samples of [redacted] products will be submitted to an independent laboratory [redacted] for stability and sterility testing. Your procedure for machine processing states that samples of the product will be submitted for stability and sterility testing from [redacted]. In both instances you are referring to the release chemistry testing and not a true stability test program, which establishes a drug's appropriate storage conditions and expiration date using a validated stability indicating method.

We acknowledge receipt of your February 5, 2002 letter responding to our FDA-483, Inspectional Observations. We find your response inadequate. Contrary to your contention in your response letter that you are operating as a retail pharmacy, our investigation finds that your firm has transcended the level of normal pharmacy operation and is operating as a drug manufacturer, as stated above. Further, while we have been informed that your firm has temporarily ceased the distribution of your "starter packs," your firm has not committed to altogether discontinuing future manufacture and distribution of such drug products.

The above deficiencies should not be construed as an all-inclusive list of violations that may be in existence at your facility and they may not be limited to the above cited drug products. It is your responsibility to ensure that all requirements of the Act and regulations promulgated thereunder are being met. Federal agencies are advised of the issuance of all Warning Letters about drugs and services so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within fifteen (15) days of receipt of this letter, stating the actions you have taken to correct these violations and to prevent future violations of

the Act. If you fail to take such action, FDA is prepared to take further actions against your firm, such are seizure and/or injunction.

Please direct your response or questions regarding this matter to Russell A. Campbell, Compliance Officer, Food and Drug Administration, San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502-7070.

Sincerely,

Dennis K. Linsley
Director, San Francisco District

Enclosures:
FDA 483

cc: Patricia Harris
California State Board of Pharmacy
400 R Street, Suite 4070
Sacramento, CA 95814